PA..NT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 25 September 2000 (25.09.00)	
International application No. PCT/US99/29593	**Applicant's or agent's file reference** ISPH-0432
International filing date (day/month/year) 14 December 1999 (14.12.99)	**Priority date** (day/month/year) 07 January 1999 (07.01.99)
Applicant ACKERMANN, Elizabeth, J. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

31 July 2000 (31.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Henrik Nyberg

Telephone No.: (41-22) 338.83.38

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07H 21/04, 21/02, C12Q 1/68, 15/63, A61K 48/00

A1

(11) International Publication Number: WO 00/40595

(43) International Publication Date: 13 July 2000 (13.07.00)

(21) International Application Number: PCT/US99/29593

(22) International Filing Date: 14 December 1999 (14.12.99)

(30) Priority Data:
09/226,568 7 January 1999 (07.01.99) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 09/226,568 (CIP)
Filed on 7 January 1999 (07.01.99)

(71) Applicant *(for all designated States except US)*: ISIS PHARMACEUTICALS, INC. [US/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ACKERMANN, Elizabeth, J. [US/US]; 519 Santa Victoria, Solana Beach, CA 92075 (US). BENNETT, C., Frank [US/US]; 1347 Cassins Street, Carlsbad, CA 92008 (US). DEAN, Nicholas, M. [GB/US]; 2110 Whisperwind Lane, Olivenhein, CA 92024 (US). MARCUSSON, Eric, G. [US/US]; 6369 Caminito de Pastel, San Diego, CA 92111 (US).

(74) Agents: LICATA, Jane, Massey et al.; Law Offices of Jane Massey Licata, 66 E. Main Street, Marlton, NJ 08053 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ANTISENSE MODULATION OF NOVEL ANTI–APOPTOTIC BCL–2–RELATED PROTEINS

(57) Abstract

Compositions and methods are provided for modulating the expression of novel anti–apoptotic bcl–2–related proteins. Antisense oligonucleotides targeted to nucleic acids encoding the human novel anti–apoptotic bcl–2–related proteins A1 and mcl–1 are preferred. Methods of using these compounds for modulation of novel anti–apoptotic bcl–2–related protein expression and for treatment of diseases associated with expression of novel anti–apoptotic blc–2–related proteins are also provided. Also provided are methods of using these compounds for promoting apoptosis and for treatment of diseases for which promotion of apoptosis is desired.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/29593

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/04, 21/02; C12Q 1/68, 15/63; A61K 48/00
US CL : 536/23.1, 24.3, 24.5; 435/6, 91.1, 375, 440; 514/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/23.1, 24.3, 24.5; 435/6, 91.1, 375, 440; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,583,034 A (GREEN et al) 10 December 1996 (10.12.1996), column 2, line 50-67.	1-11, 13, 21-23
Y	CHAO J. R. mcl-1 Is an Immediate-Early Gene Activated by the Granulocyte-Macrophage Colony -Stimulating Factor(GM-CSF) Signaling Pathway and Is One Component of the GM-CSF Viability Response. Molecular and Cellular Biology. August 1998, Vol. 18. No. 8, pages 4883-4898, especially page 4894.	1-11, 13, 21-23
A	CROOKE S. T. Basic Principles of Antisense Therapeutics. In: Antisense Research And Applications, Chapter 1, Springer-Verlag Press, Berlin, Heidelber, New York July 1998 pages 1-50, especially page 2-3	1-41

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2000 (11.02.2000)	29 FEB 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer George Elliott Telephone No. 703-308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/29593

Continuation of B. FIELDS SEARCHED Item 3: USPAT, EPO, JPO, CaPlus
search terms: antisense, ribozyme, aptamer, triplex, bcl?, bcl-2, apoptosis

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

PCT

WRITTEN OPINION

(PCT Rule 66)

	Date of Mailing (*day/month/year*) 08 NOV 2000
Applicant's or agent's file reference ISPH-0432	REPLY DUE within 2 months/days from the above date of mailing

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US99/29593	14 December 1999 (14.12.1999)	07 January 1999 (07.01.1999)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07H 21/04, 21/02; C12Q 1/68; A61K 48/00 and US Cl.: 536/23.1, 24.3, 24.5,; 435/6, 91.1, 375; 514/44

Applicant

ISIS PHARMACEUTICALS, INC.

1. This written opinion is the first (first, etc,) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07 ~~May 2001~~ (07.05.2001) .

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer George Elliott Telephone No. 703-308-0196

Form PCT/IPEA/408 (cover sheet)(July 1998)

WRITTEN OPINION

International application No.
PCT/US99/29593

I. Basis f the pinion

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-70, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 71-75, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-9, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE _____

☐ the claims, Nos. NONE _____

☐ the drawings, sheets~~/fig~~ NONE _____

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

WRITTEN OPINION

International application No.
PCT/US99/29593

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step r industrial applicability; citations and explanati ns supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-41	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	12, 14-20, 24-41	YES
	Claims	1-11, 13 , and 21-23	NO
Industrial Applicability (IA)	Claims	1-41	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-11, 13, 21-23 lack an inventive step under PCT Article 33(3) as being obvious over Green et al., Chao, or KOREA GREEN CROSS CORPORATION in view of Uhlmann et al.

Green et al. teach a method for enhancing apoptosis in cells by treating the cells with antisense oligonucleotides which hybridizes to a known anti-apoptotic gene such as bcl2 and bcr-abl (col.2, lines 50-67). Green et al. designed antisense oligonucleotide of 18 nucleotides in length targeting bcr-abl (col. 2 lines 65-67).

Chao et al. teach the use of antisense constructs in the inhibition of *mcl-1* leading to an induction of apoptosis in TF-1 myeloid progenitor cells (p. 4893).

Neither reference above, specifically teach the design of antisense oligonucleotides of 8 to 30 nucleotides targeting *mcl-1* or human A1.

Uhlmann teach the design of antisense nucleic acids of 8 to 30 nucleotides in order to facilitate binding of the antisense molecule to its target mRNA and increase the uptake of the antisense molecule into a cell.

Therefore in view of the methods of designing antisense oligonucleotides to target anti-apoptotic cells taught by Green et al., and the ability of the antisense constructs to inhibit the expression of *mcl-1* in TF-1 myeloid precursor cells and result in the triggering of apoptosis in these cells as taught by Chao et al., and the teaching of Uhlmann which disclose the efficacy of antisense oligonucleotides of 8 to 30 nucleotides in the targeting of a mRNA molecule to inhibits its function in a cell. It would have been prima facie obvious to one of ordinary skill in the art at the time of filing of the instant application to design antisense oligonucleotides of 8 to 30 nucleotides targeting *mcl-1* and human A1 expression in order to regulate apoptosis in a cell.

Claims 12, 14-20, 24-41 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the specific antisense oligonucleotides targeting nucleic acid encoding human A1 or human mcl-1 disclosed by Applicants or the methods of using said antisense oligonucleotides in a method of treating a patient having a disease associated with the expression of human A1 or mcl-1.

---------- NEW CITATIONS ----------

WO 96-30513 A1 (KOREA GREEN CROSS CORPORATION) 03 October 1996, see entire document.

UHLMANN et al. Antisense oligonucleotides: A New therapeutic principle, Chemical Reviews. June 1990, Vol. 90, Number 4, pages 544-560.

WRITTEN OPINION

International application No.

PCT/US99/29593

VIII. Certain bservations on the internati nal application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention. Th description fails to adequately describe the pharmaceutical compositions comprising antisense compounds targeting nucleic acid encoding an anti-apoptotic bcl-2-related protein, and the methods of using said compositions. In view of the lack of adequate guidance and instruction regarding the use of the claimed compositions, and the practice of the claimed methods, the lack of representative working examples demonstrating the therapeutic efficacy of the claimed compositions, and the unpredictability regarding the behavior of antisense oligonucleotides *in vivo*, one of skill in the art would not be able to practice the present invention without undue experimentation.

Claims 15-20 and 24-33 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.

WRITTEN OPINION

International application No.
PCT/US99/29593

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

Docket System ✓
Status Report ✓
Docket Book ✓
NP- 7-7-01

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	21 FEB 2001

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
ISPH-0432	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/29593	14 December 1999 (14.12.1999)	07 January 1999 (07.01.1999)

Applicant

ISIS PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Janet L Epps
Facsimile No. (703)305-3230	Telephone No. 703-308-0196

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ISPH-0432	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/29593	International filing date *(day/month/year)* 14 December 1999 (14.12.1999)	Priority date *(day/month/year)* 07 January 1999 (07.01.1999)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07H 21/04, 21/02; C12Q 1/68; A61K 48/00 and US Cl.: 536/23.1, 24.3, 24.5,; 435/6, 91.1, 375; 514/44		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31 JULY 2000 (31.07.2000)	01 February 2001 (01.02.2001)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Janet L Epps Telephone No. 703-308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/29593

I. Basis f the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-70 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 71-75 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☐ the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-9 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/29593

V. Reasoned statement under Articl 35(2) with regard to novelty, inventive step r industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-41	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	12, 14-20, 24-41	YES
	Claims	1-11, 13 , and 21-23	NO
Industrial Applicability (IA)	Claims	1-41	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Claims 1-11, 13, 21-23 lack an inventive step under PCT Article 33(3) as being obvious over Green et al. , Chao, or KOREA GREEN CROSS CORPORATION. in view of Uhlmann et al.

Green et al. teach a method for enhancing apoptosis in cells by treating the cells with antisense oligonucleotides which hybridizes to a known anti-apoptotic gene such as bcl2 and bcr-abl (col.2, lines 50-67). Green et al. designed antisense oligonucleotide of 18 nucleotides in length targeting bcr-abl (col 2 lines 65-67).

Chao et al. teach the use of antisense constructs in the inhibition of *mcl-1* leading to an induction of apoptosis in TF-1 myeloid progenitor cells (page 4893).

Neither reference above, specifically teach the design of antisense oligonucleotides of 8 to 30 nucleotides targeting *mcl-1* or human A1.

Uhlmann teach the design of antisense nucleic acids of 8 to 30 nucleotides in order to facilitate binding of the antisense molecule to its target mRNA and increase the uptake of the antisense molecule into a cell.

Therefore in view of the methods of designing antisense oligonucleotides to target anti-apoptotic cells taught by Green et al., and the ability of the antisense constructs to inhibit the expression of *mcl-1* in TF-1 myeloid precursor cells and result in the triggering of apoptosis in these cells as taught by Chao et al., and the teaching of Uhlmann which disclose the efficacy of antisense oligonucleotides of 8 to 30 nucleotides in the targeting of a mRNA molecule to inhibits its function in a cell. It would have been prima facie obvious to one of ordinary skill in the art at the time of filing of the instant application to design antisense oligonucleotides of 8 to 30 nucleotides targeting *mcl-1* and human A1 expression in order to regulate apoptosis in a cell.

Claims 12, 14-20, 24-41 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the specific antisense oligonucleotides targeting nucleic acid encoding human A1 or human mcl-1 disclosed by Applicants or the methods of using said antisense oligonucleotides in a method of treating a patient having a disease associated with the expression of human A1 or mcl-1.

——————— NEW CITATIONS ———————

WO 96-30513 A1 (KOREA GREEN CROSS CORPORATION) 03 October 1996, see entire document.

Uhlman et al., Antisense oligonucleotides: A New therapeutic principle, Chemical Reviews, June 1990, Vol. 90, Number 4, pages 544-560.

VIII. Certain bservations on the internati nal application

The foll wing observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention. The description fails to adequately describe the pharmaceutical compositions comprising antisense compounds targeting nucleic acid encoding an anti-apoptotic bcl-2-related protein, and the methods of using said compositions. In view of the lack of adequate guidance and instruction regarding the use of the claimed compositions, and the practice of the claimed methods, the lack of representative working examples demonstrating the therapeutic efficacy of the claimed compositions, and the unpredictability regarding the behavior of antisense oligonucleotides *in vivo*, one of skill in the art would not be able to practice the present invention without undue experimentation.

Claims 15-20 and 24-33 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.